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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,081	04/06/2001	Satoru OI	2559US0P	2326

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EXAMINER	
ROBINSON, BINTA M	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,081	OL ET AL.	
	Examiner	Art Unit	
	Binta M Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7,9,13-15,17,18,21 and 24-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 28-30 is/are allowed.

6)☒ Claim(s) 1-7,9,13-15,17,18,21,24-27, 31, 32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-7, 9, 13-15, 17-18, 21, 24-32 are now pending in the application.

The examined elected subject matter reads on claims 1, 2, 3, 4, 5, 6, 7, 9, 13, 14, 15, 17, 18, 21, 24, 25, 26, 27, 28, 29, 30, 31, 32 drawn to the compound of formula I in claim 1 wherein Y is equal to 2 H atoms, D is as claimed, E is as claimed, G is as claimed, Z is as claimed, A is a phenyl ring optionally substituted as claimed, B is a phenyl ring which is optionally substituted or a cycloalkane ring, L is an alkyl group optionally substituted as claimed, but not optionally interrupted by O or S, or a chemical bond, X is as claimed, R2 is an optionally substituted amino group, the method of treating with this compound, a method of producing this compound according to formula Ia, and a pharmaceutical composition containing said compound.

In the office action mailed 5/18/04, the examiner stated that claims 1, 2, 3, 4, 5, 6, 7, 9, 21, 24, 26, 28, 29, 30, 31, and 32 are allowable as they read on the examined subject matter. However, claims 1, 2, 3, 4, 5, 6, 7, 9, 21, 24, 26, 28, 29, 30, 31, and 32 have not been found allowable in this office action because of 112, first paragraph and second paragraph issues that are discussed below in this action.

Applicant's request clarification to the status of claim 18. Although claim 18 does not contain any of the language that was rejected under 112, second paragraph in the office action mailed 5/18/04 and the 112, second paragraph rejection made in the office action mailed 5/18/04 is removed, it is rejected below for 112, second paragraph problems.

The rejections of claim 17 made in the office action mailed 5/18/04 has been maintained despite applicant's remarks revealing that claim 17 is intended to be a dependent claim. Claim 17 still reads as an independent claim because no language exists which states that the compound being made is the compound "according to claim 1". It is only stated that the radicals A, B, X, Y, L, D, G, Z, R1, R2 and Ra have the same meanings as in claim 1. Claim 17 is not written in proper dependent claim format.

Applicants also traverse the 112, second paragraph rejection of the phrase "wherein the symbols have the same meanings as above", asserting that those skilled in the art would understand that "above" refers to information provided earlier in the claim. However, applicants also assert that claim 17 is a dependent claim. How would one skilled in the art know whether or not the meanings are defined above at claim 17 or in preceding claim 1? Reference can be made to the radicals being defined according to the definitions for these radicals in claim 1.

Applicant's also traverse the rejection of the phrase "complications of diabetes" in claims 25 and 31, asserting that this phrase is common in the art and would be understood by one skilled in the art. However, "complications of diabetes" is not the same thing as "diabetes". Additionally, "complications of diabetes" is not further described in the specification, so therefore, it is not apparent as to what complications of diabetes are being claimed.

(old rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

D. In claim 17, lines 1-2, page 9, and all other occurrences throughout the claim, the phrase "wherein the symbols", have the same meanings as in claim 1 is unclear. Claim 17 is a dependent claim, so therefore, the meanings of these radicals must be defined at claim 17.

In claim 17 the phrase "wherein the symbols have the same meanings as above" is ambiguous. Is the applicant referring to the symbols having the same meanings in preceding claims, within the same claim or in the specification? All radicals and symbols must be defined at claim 17.

B. In claim 25, page 15 line 1, and in claim 31, page 20 line 1, the phrase "complications of diabetes" is ambiguous. Treating complications of diabetes is not the same thing as treating diabetes. What complications of diabetes is the applicant referring to?

(new rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 3, 4, 5, 6, 7, 9, 13, 14, 15, 17, 18, 21, 24, 25, 26, 27, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 5, page 3, and all other occurrences throughout claims 1, 2, 3, 4, 5, 6, 7, 9, 13, 14, 15, 17, 18, 21, 24, 25, 26, 27, the term "optionally substituted cyclic group" is indefinite. What cyclic groups are intended?

B. In claim 1, line 3, and all other occurrences throughout claims 2, 3, 4, 5, 6, 7, 9, 13, 15, 17, 18, 21, 24, 25, 26, 27 the phrase "homocyclic aromatic ring" is unclear. At page 286, In the Hack's Chemical Dictionary, the term "homocyclic" is defined as pertaining to compounds which contain a closed chain or ring of atoms of the same type usually C atoms. It is not clear if the applicant is claiming a heterocyclic or carbocylic ring, since the specification does not further delineate what rings homocyclic rings can be in the instant invention.

C. Claim 4 recites the limitation "piperidinyl" in line 2. There is insufficient antecedent basis for this limitation in the claim.

D. Claim 17 is not a proper dependent claim. The process as claimed does not make all the compounds of claim 1. All definitions have to be positively. In claim 17, line 7, page 9, the phrase "reactive derivative" is unclear. A derivative is not the same chemical species as the compound of formula IIa. It is not clear what compounds are being claimed when the reactive derivative is not being claimed since these reactive derivatives are not further defined in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 26, 31, 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes and obesity with the instant compounds, does not reasonably provide enablement for a method of treating all diabetic complications or intractable diarrhea. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 25, 26, 31, and 32 is to treat diabetic complications, and intractable diarrhea with the instant compounds.

The State of the Prior Art

The state of the art is that somatostatin is a neuropeptide originally isolated from the hypothalamus as a growth hormone inhibitory substance and is now known to be a multifunctional peptide located in most brain regions as well as in

peripheral organs. See page 1249 of Patel et. al. (See Reference U)

Type I to type V somatostatin receptors are known in the art and are expressed for different functions in the central and peripheral sites of the body. See page 2, lines 1-3 of the specification. Not all types of somatostatin have the same property and are used in the same way. Some somatostains inhibit the secretion of pituitary and digestive canal hormones, while others inhibit gastric acid secretion. See lines 16-25 of the specification. Somatostatin analogues have limited clinical use in treating diarrheas. See PubMed ID abstract: 7605866 (Schiller et. al., See reference V) The somatostatin octapeptide analogue octreotide decreases the tonic response of the descending colon, but paradoxically increases phasic motility in the descending colon and rectum in diarrhea. The overall effect of relatively low doses of octreotide on colonic transit was not significant. See page 293 of Ford (See Reference W). Somatostatin analogues have been shown to be useful in treating obesity and diabetes and some but not all diabetic complications. The Somatostatin analog octreotide inhibited insulin secretion in patients with hypothalamic obesity resulting in weight loss and an improved quality of life. Octreotide also retarded the progression of the microvascular complications in pre-proliferative and advanced stages of diabetic retinopathy. See Caplus abstract number 2003:435886, (Boehm et. al.) (See Reference X). Octreotide suppresses GH levels in patients with diabetes mellitus and postprandial blood glucose increases in these patients with the use of Octreotide. (See PubMed Abstract: 7997211), (See Reference U1). Renal

disease is often a complication of diabetes, however, somatostatin analogues have only reached the clinical stage of testing in human subjects and their pharmaceutical efficacy in the treatment of renal disease is not certain. See page 259 of Johnson, Reference V1).

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since no real correlation has been shown between somatostatin inhibition and the diseases or conditions disclosed claimed other than obesity and diabetes.

Hence, in the absence of a showing of correlation between all the diseases or conditions (other than diabetes and obesity) claimed as capable of treatment by the compound of claim 1 and the regulation of somatostatin, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of somatostatin, in the treatment of the diabetic complications and intractable diarrhea.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high

level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can regulate somatostatin function which helps in the treatment for diabetic complications, obesity and intractable diarrhea. However, the specification fails to provide guidance as to whether the diabetic complications listed as somatostatin-mediated conditions other than diabetes and obesity, require the regulation of somatostatin for treatment. Several of the compounds have been made. However, no evidence is presented which shows the correlation between the regulation of somatostatin and the diseases other than diabetes and obesity.

The breadth of the claims

The breadth of the claims 25, 26, 31, and 32 is that the instant can treat any diabetic complication, and intractable diarrhea.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by regulation of somatostatin and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the regulation of somatostatin.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the instant compound for the treatment of an somatostatin-mediated disease or condition other than diabetes and obesity. As a result necessitating one of skill to perform an exhaustive search for which somatostatin-mediated condition can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which somatostatin-mediated conditions can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 6, 7, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Girault et. al. (See Reference W1). Girault teaches for examples, compounds, 8a, 8b, 8c, 8d, 8e, 8f, 8j, 8k, 8l. At page 1178, see for example, the Girault compounds 8a, 8b, 8c, 8d, 8e, 8f, 8j, 8k, 8l.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-562.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

Cecilia Tsang

Cecilia J. Tsang
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